REMARKS

Claims 53-55, 61-66, and 70 have been amended. Claims 68 and 69 have been cancelled without prejudice to their subsequent reintroduction into this application or their introduction into a related application. Upon entry of this paper, claims 53-67 and 70-72 will be pending and under consideration.

Claims 53-55, 61-66, and 70 have been amended to correct antecedents, grammar and punctuation. In addition, claim 53 has been amended to introduce the limitations of now cancelled claims 68 and 69. Claims 65 and 70 have been amended to further clarify that the span of the spray plume is defined by the term Dv90-Dv10/Dv50 (see last two full paragraphs appearing on page 10 of Preliminary Amendment A filed October 5, 2005 for the units of the term "span"). As a result, the term span is a ratio without units. In addition, support for the amendment to claim 64 can be found in the second to last full paragraph appearing on page 10 of Preliminary Amendment A filed October 5, 2005, where Applicant indicated that the features of the plume geometry are inherent in the device tested in Example 1 of the application. Applicant believes that the amendments introduce no new matter.

The outstanding rejections are addressed in the order in which they appear in the Office action.

Rejections Under 35 U.S.C. § 112, 2nd Paragraph

According to pages 2-4 of the outstanding Office action, claims 53-72 presently stand rejected under 35 U.S.C. § 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as his invention.

Applicant believes that the amendments to claims 53, 54, 62-67, and 70, and the explanation for the lack of units in claims 65 and 70 address the rejections noted in the Office action. Accordingly, Applicant respectfully requests that the rejection of pending claims 53-72 be reconsidered and withdrawn.

Rejection of Claims 53-59 and 62-71 Under 35 U.S.C. § 103(a)

According to pages 4-9 of the outstanding Office action, claims 53-59 and 62-71 presently stand rejected under 35 U.S.C. § 103(a) as being obvious over U.S. Patent No. 5,437,267 to Weinstein *et al.* (hereinafter "Weinstein") and Published U.S. Patent Application Publication No. US 2001/0004644 A1 to Levin (hereinafter "Levin") in view of Ward-Smith in Nasal Spray Testing, Pharmaceutical Technology Europe (2002) pages 1-9 (hereinafter "Ward-Smith"). In addition, it appears that the Office also relied upon certain product information for Stadol NS®, which is an aqueous solution of butorphanol tartarate for administration as a metered spray to the nasal mucosa.

The Office alleges that it would be prima facie obvious to modify the device and medicament administered in Weinstein to an opioid. The Office goes on to say that the motivation to combine the references would be obvious based on Ward-Smith, which teaches specific parameters for efficacious administration. Claims 68 and 69 have been cancelled thereby rendering the rejection of these claims moot. Applicant respectfully traverses the rejection to the extent that it is maintained over claims 53-59, 62-67 and 70-71, as amended, in view of the following comments.

Under 35 U.S.C. § 103(a), an invention is unobvious if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would not have been obvious at the time the invention was made to a person having ordinary skill in the art. Applicant submits that the case law makes clear that the subject matter, taken as a whole, must be considered when evaluating the obviousness of a claimed invention. For the following reasons, Applicant submits that the claimed subject matter, taken as a whole, was not described in the applied references, and that it was the features of the claimed device that lead to the unexpected properties described in Example 1 of the application.

Weinstein describes a device for the intranasal delivery of a medicament to the nasal membranes for the treatment of conditions such as rhinitis. (See, abstract.) The Office acknowledges that Weinstein does not teach the use of an opioid formulation in such a device, the detection of droplet size distribution or a specific droplet size. Applicant submits

that Weinstein fails to describe an opioid containing device, which upon positioning 5 cm away from a laser beam detection pathway, actuating the device to produce a spray plume perpendicular to said pathway, and detecting droplet size distribution of the spray plume with said laser beam detection pathway, produces a spray plume having a Dv10 of from about 14.3 μm to about 17.1 μm and a Dv50 of from about 31.0 μm to about 35.3 μm.

Levin teaches intranasally administering to a patient a pharmaceutical composition comprising a local anesthetic. (See, abstract). Levin teaches that his "invention relates to a method of inhibiting cephalic inflammation, such as that associated with a CNvD in a human patient. This method comprises intranasally (preferably doronasally) administering to the patient a long-acting local anesthetic pharmaceutical composition in an amount effective to inhibit the cephalic inflammation." (See, ¶59.) Although Levin describes the administration of butorphanol tartarate as well as other agents (see, ¶18), Levin in the very next sentence states that the administration "of any combination of these compounds has not offered satisfactory or sustained relief from the pain or other symptoms associated with an acute migraine episode in many patients." *Id.*

The Office acknowledges that Levin does not teach the detection of droplet size distribution or a specific droplet size. Applicant submits that Levin fails to describe an opioid containing device, which upon positioning 5 cm away from a laser beam detection pathway, actuating the device to produce a spray plume perpendicular to said pathway, and detecting droplet size distribution of the spray plume with said laser beam detection pathway, produces a spray plume having a Dv10 of from about 14.3 μm to about 17.1 μm and a Dv50 of from about 31.0 μm to about 35.3 μm.

The Office appears to be relying upon the teachings of Ward-Smith to make up for the deficiencies in Weinstein and Levin. Applicant agrees that Ward-Smith describes certain measurements for characterizing spay plumes, for example, Dv10, Dv50 and Dv90 measurements. However, Ward-Smith is completely silent about the particular plume geometry that should be created to provide the results described in Example 1 of the application. Applicant submits that none of the applied references, either alone or in combination, teach an opioid containing device, which upon positioning 5 cm away from a

laser beam detection pathway, actuating the device to produce a spray plume perpendicular to said pathway, and detecting droplet size distribution of the spray plume with said laser beam detection pathway, produces a spray plume having a Dv10 of from about 14.3 μm to about 17.1 μm and a Dv50 of from about 31.0 μm to about 35.3 μm.

In Example 1, Applicant clearly demonstrates that the test device (the unit dose system), which produces the claimed plume geometry, provides an unexpectedly higher butorphanol concentration in the blood plasma relative to the prior art, multi-dose device. See, for example, Figure 1 and the discussion of Figure 1 appearing on page 16 of the application. In particular, page 16, lines 7-9 of the application (as amended by Preliminary Amendment A) states, "[t]he mean levels of butorphanol from analysis of the subject's blood plasma reported in pg/ml are plotted against time in Figures 1 and 2. The concentration of drug for the unit-dose system was unexpectedly higher than that of the multi-dose system."

In addition, the application on page 18, lines 14-21 (as amended in Preliminary Amendment A) states, "the test device achieves 10% higher area under the curve and 10% higher serum levels as compared to the reference device. This difference is highly significant from a patient therapy standpoint. When FDA-prescribed bioequivalence statistical methods are applied, it is concluded that-the products as administered to the patients are not equivalent. Thus, the unit-dose device in one embodiment of the present invention provides an unexpected improvement in the intranasal administration of butorphanol."

Applicant submits that the features of the claimed device that produces the requisite plume geometry, as associated with the unexpected properties noted above, are neither taught nor suggested in the applied references, either alone or in combination. Accordingly, Applicant submits that the subject matter of claim 53, taken as a whole, would not have been obvious to the skilled artisan at the time the invention was made. Accordingly, Applicant respectfully requests that the rejection of claim 53 be reconsidered and withdrawn.

Claims 54-59, 62-67, and 70-71, depend from and, therefore, incorporate all the limitations of claim 53. In view of the remarks relating to claim 53, Applicant respectfully

requests that the rejection of claims 54-59, 62-67, and 70-71 also be reconsidered and withdrawn.

Rejection of Claims 60, 61 and 72 Under 35 U.S.C. § 103(a)

According to pages 9-10 of the outstanding Office action, claims 60, 61 and 72 presently stand rejected under 35 U.S.C. § 103(a) as being obvious over Illum *et al.* in J. Pharmacol. Exp. Therapeutics (2001) 301: 391-400 (hereinafter "Illum"), Pezron *et al.* in (Expert Opin. Ther. Patents (2002) 12: 331-340 (hereinafter "Pezron"), Mansjushree *et al.* in Can. J. Anesth. (2002) 49: 190-193 (hereinafter "Mansjushree") in view of U.S. Patent No. 6,127,385 to Midha *et al.* (hereinafter "Midha"). Applicant respectfully traverses the rejection to the extent that it is maintained over claims 60, 61 and 72, as amended, in view of the following comments.

Claims 60, 61 and 72 depend from and, therefore, incorporate all the limitations of independent claim 53. Applicant submits that claim 53 and, therefore, claims 60, 61 and 72, all require an opioid containing device, which upon positioning 5 cm away from a laser beam detection pathway, actuating the device to produce a spray plume perpendicular to said pathway, and detecting droplet size distribution of the spray plume with said laser beam detection pathway, produces a spray plume having a Dv10 of from about 14.3 μm to about 17.1 μm and a Dv50 of from about 31.0 μm to about 35.3 μm. Applicant submits that the benefits of an opioid containing device that provides such a plume geometry are described in Example 1 of the application, and that none of these features are described in the applied references.

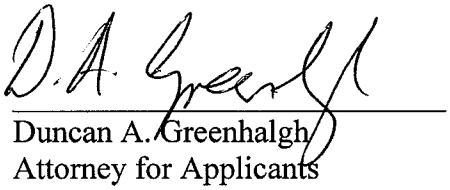
Accordingly, Applicant submits that the applied references fail to teach or suggest the claimed subject matter, taken as a whole. As a result, Applicant respectfully requests that this rejection be reconsidered and withdrawn.

CONCLUSION

Applicant believes that, in the view of the above amendments and remarks, the pending claims are in condition for allowance. Early favorable action is respectfully

solicited. The Office is invited to contact the undersigned with any questions about this submission.

Respectfully submitted,



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